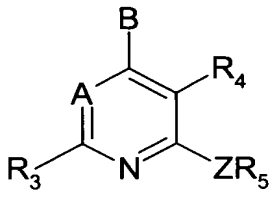
CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

A is N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_1$, $-CHR_1OR_2$, $-CHR_2SR_1$, $-C(S)R_2$, $-C(O)R_2$, $-CHR_2NR_1R_2$, $-CHR_1NHR_2$, $-CHR_1N(CH_3)R_2$, or $-NR_{12}NR_1R_2$;

Z is NH, O, S, $-N(C_1-C_2$ alkyl), $-NC(O)CF_3$, or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl, or $-C(R_{13}R_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R_5, which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR_{12}, and $S(O)_m$, and optionally comprises from one to three double bonds, and is optionally substituted with halo, C_1-C_4 alkyl, $-O(C_1-C_4$ alkyl), NH_2, $NHCH_3$, $N(CH_3)_2$, CF_3, or OCF_3, with the proviso that said ring does not contain any –S-S-, -S-O-, -N-S-, or –O-O- bonds, and does not comprise more than two oxygen or $S(O)_m$ heterologous members;

R_1 is C(O)H, $C(O)(C_1-C_6$ alkyl), $C(O)(C_1-C_6$ alkylene)$(C_3-C_8$ cycloalkyl), $C(O)(C_3-C_8$ cycloalkylene)$(C_3-C_8$ cycloalkyl), $C(O)(C_1-C_6$ alkylene)$(C_4-C_8$ heterocycloalkyl), $-C(O)(C_3-C_8$ cycloalkylene)$(C_4-C_8$ heterocycloalkyl), C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_4-C_8 heterocycloalkyl, $-(C_1-C_6$ alkylene)$(C_3-C_8$ cycloalkyl), $-(C_3-C_8$ cycloalkylene)$(C_3-C_8$ cycloalkyl), $-(C_1-C_6$ alkylene)$(C_4-C_8$ heterocycloalkyl), $-(C_3-C_8$ cycloalkylene)$(C_4-C_8$ heterocycloalkyl), or –O-aryl, or $-O-(C_1-C_6$ alkylene)-aryl; wherein said aryl, C_4-C_8 heterocycloalkyl, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylene, and C_1-C_6 alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R_8 independently selected from the group consisting of C_1-C_4 alkyl, $-C_3-C_8$ cycloalkyl, hydroxy, chloro, bromo, iodo, CF_3, $-O-(C_1-C_6$ alkyl), $-O-(C_3-C_5$ cycloalkyl), $-O-CO-(C_1-C_4$ alkyl), $-O-CO-NH(C_1-C_4$ alkyl), $-O-CO-N(R_{24})(R_{25})$, $-N(R_{24})(R_{25})$, $-S(C_1-C_4$ alkyl), $-S(C_3-C_5$ cycloalkyl), $-N(C_1-C_4$alkyl)$CO(C_1-C_4$ alkyl), $-NHCO(C_1-C_4$ alkyl), $-COO(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl),

-CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -OSO_2(C_1-C_4 alkyl), S^+(C_1-C_6 alkyl)(C_1-C_2 alkyl)I^-, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl); and wherein the C_1-C_6 alkyl, C_1-C_6 alkylene, C_5-C_8 cycloalkyl, C_5-C_8 cycloalkylene, and C_5-C_8 heterocycloalkyl moieties of R_1 may optionally independently contain from one to three double or triple bonds; and wherein the C_1-C_4 alkyl moieties and C_1-C_6 alkyl moieties of R_8 can optionally independently be substituted with hydroxy, amino, C_1-C_4 alkyl, aryl, -CH_2-aryl, C_3-C_5 cycloalkyl, or –O-(C_1-C_4 alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl group of R_1 contains from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and NR_{12};

Sub A1 Cont.

R_2 is hydrogen, C_1-C_{12} alkyl, C_3-C_8 cycloalkyl, C_4-C_8 heterocycloalkyl, -(C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), -(C_1-C_6 alkylene)(C_4-C_8 heterocycloalkyl), -(C_3-C_8 cycloalkylene)(C_4-C_8 heterocycloalkyl), aryl, –(C_1-C_6 alkylene)aryl, or -(C_3-C_8 cycloalkylene)(aryl); wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1-C_6 alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C_1-C_6 alkoxy, -OH, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$S(O)_2$(C_1-C_6 alkyl), S^+(C_1-C_6 alkyl)(C_1-C_2 alkyl)I^-, CN, and NO_2; and wherein the C_1-C_{12} alkyl, -(C_1-C_6 alkylene), -(C_5-C_8 cycloalkyl), -(C_5-C_8 cycloalkylene), and -(C_5-C_8 heterocycloalkyl) moieties of R_2 may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl group of R_2 contains from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and NR_{12};

or when R_1 and R_2 are as in –NHCHR_1R_2, -OCHR_1R_2, -SCHR_1R_2, –CHR_1R_2 or -NR_1R_2, R_1 and R_2 of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, $S(O)_m$, nitrogen or NR_{12}; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, CF_3, -O-(C_1-C_4 alkyl), -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl),-COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -OSO_2(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), and –SO_2(C_1-C_4 alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, NH_2, NH(C_1-C_2 alkyl), $N(CH_3)_2$, -$NHCOCF_3$, -$NHCH_2CF_3$, $S(O)_m$(C_1-C_4 alkyl), $CONH_2$, -$CONHCH_3$, $CON(CH_3)_2$, -CF_3, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, -(C_1-C_4 alkylene)(C_3-C_5 cycloalkyl), -(C_3-C_5 cycloalkylene)(C_3-C_5 cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR_{24}, C_1-C_6 alkoxy, -O-(C_3-C_5 cycloalkyl), -O-(C_1-C_4 alkylene)(C_3-C_5 cycloalkyl), -O-(C_3-C_5 cycloalkylene)(C_3-C_5 cycloalkyl), -

$CH_2SC(S)O(C_1$-C_4 alkyl), -CH_2OF_3, CF_3, amino, nitro, -$NR_{24}R_{25}$, -(C_1-C_4 alkylene)-OR_{24}, -(C_1-C_4 alkylene)Cl, -(C_1-C_4 alkylene)$NR_{24}R_{25}$, -$NHCOR_{24}$, -$NHCONR_{24}R_{25}$, -$C{=}NOR_{24}$, -$NHNR_{24}R_{25}$, -$S(O)_mR_{24}$, -$C(O)R_{24}$, -$OC(O)R_{24}$, -C(O)CN, -$C(O)NR_{24}R_{25}$, -$C(O)NHNR_{24}R_{25}$, and –$COOR_{24}$, wherein the alkyl and alkylene groups of R_4 may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R_{10} independently selected from hydroxy, amino, -$NHCOCH_3$, -$NHCOCH_2Cl$, -$NH(C_1$-C_2 alkyl), -$N(C_1$-C_2 alkyl)(C_1-C_2 alkyl), -$COO(C_1$-C_4 alkyl), -COOH, -$CO(C_1$-C_4 alkyl), C_1-C_6 alkoxy, C_1-C_3 thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

Sub A1 cont.

R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, C_1-C_{10} alkyl, -(C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_1-C_4 alkylene)(C_4-C_8 heterocycloalkyl), -(C_3-C_8 cycloalkyl), -(C_4-C_8 heterocycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_4-C_8 heterocycloalkyl), C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, nitro, cyano, -$NR_{24}R_{25}$, -$NR_{24}COR_{25}$, -$NR_{24}CO_2R_{26}$, -COR_{24}, -OR_{25}, -$CONR_{24}R_{25}$, -$CO(NOR_{22})R_{23}$, -CO_2R_{26}, -$C{=}N(OR_{22})R_{23}$, and –$S(O)_mR_{23}$; wherein said C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, (C_1-C_4 alkylene), (C_3-C_8 cycloalkyl), (C_3-C_8 cycloalkylene), and (C_4-C_8 heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected form C_1-C_4 alkyl, C_3-C_8 cycloalkyl, (C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), C_1-C_4 haloalkyl, hydroxy, C_1-C_6 alkoxy, nitro halo, cyano, -$NR_{24}R_{25}$, -$NR_{24}COR_{25}$, $NR_{24}CO_2R_{26}$, -COR_{24}, -OR_{25}, -$CONR_{24}R_{25}$, CO_2R_{26}, -$CO(NOR_{22})R_{25}$, and –$S(O)_mR_{23}$; and wherein two adjacent substituents of the R_5 group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R^5, which ring optionally can contain one, two, or three heterologous members independently selected from O, $S(O)_m$, and N, but not any –S-S-, -O-O-, -S-O-, or –N-S- bonds, and which ring is optionally substituted with C_1-C_4 alkyl, C_3-C_8 cycloalkyl, -(C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cyloalkylene)(C_3-C_8 cycloalkyl), C_1-C_4 haloalkyl, nitro, halo, cyano –$NR_{24}R_{25}$, $NR_{24}COR_{25}$, $NR_{24}CO_2R_{26}$, -COR_{24}, -OR_{25}, -$CONR_{24}R_{25}$, CO_2R_{26}, -$CO(NOR_{26})R_{25}$, or –$S(O)_mR_{23}$; wherein one of said one to four optional substituents R_{27} can further be selected from -$SO_2NH(C_1$-C_4 alkyl), -$SO_2NH(C_1$-C_4 alkylene)(C_3-C_8 cycloalkyl), -$SO_2NH(C_3$-C_8 cycloalkyl), -$SO_2NH(C_3$-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), -$SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2(C_1$-C_4 alkyl), -$NHSO_2(C_3$-C_8 cycloalkyl), -$NHSO_2(C_1$-C_4 alkylene)(C_3-C_8 cycloalkyl), and -$NHSO_2(C_3$-C_8 cycloalkylene)(C_3-C_8 cycloalkyl); and wherein the alkyl, and alkylene groups of R_5 may independently optionally contain one double or triple bond;

R_{11} is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl;

R_{22} is independently at each occurrence selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), and (C_1-C_4 alkylene)(C_3-C_8 cycloalkyl);

R_{23} is independently at each occurrence selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_8 cycloalkyl, -(C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), aryl, -(C_1-C_4 alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

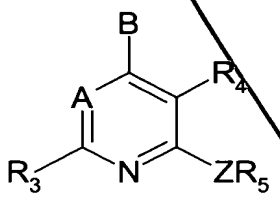
R_{24} and R_{25} are independently at each occurrence selected from hydrogen, -C_1-C_4 alkyl, C_1-C_4 haloalkyl, especially CF_3, $-CHF_2$, CF_2CF_3, or CH_2CF_3, -(C_1-C_4 alkylene)OH, -(C_1-C_4 alkylene)-O-(C_1-C_4 alkyl), -(C_1-C_4 alkylene)-O-(C_3-C_5 cycloalkyl), C_3-C_8 cycloalkyl, -(C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), -C_4-C_8 heterocycloalkyl, -(C_1-C_4 alkylene)(C_4-C_8 heterocycloalkyl), -(C_3-C_8 cycloalkylene)(C_4-C_8 heterocycloalkyl), aryl, and -(C_1-C_4 alkylene)(aryl), wherein the -C_4-C_8 heterocycloalkyl groups can each independently optionally be substituted with aryl, CH_2-aryl, or C_1-C_4 alkyl, and can optionally contain one or two double or triple bonds; or, when R_{24} and R_{25} are as $NR_{24}R_{25}$, -$C(O)NR_{24}R_{25}$, -(C_1-C_4 alkylene)$NR_{24}R_{25}$, or -$NHCONR_{24}R_{25}$, then $NR_{24}R_{25}$ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from $S(O)_m$, oxygen, nitrogen, and NR_{12}, and optionally containing from one to three double bonds;

R_{26} is independently at each occurrence selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_4 alkylene)(C_3-C_8 cycloalkyl), -(C_3-C_8 cycloalkylene)(C_3-C_8 cycloalkyl), aryl, and -(C_1-C_4 alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I, II, or III do not comprise any –S-S-, -S-O-, -N-S-, or –O-O- bonds, and do not comprise more than two oxygen or $S(O)_m$ heterologous members.

2. A compound according to claim 1 of the formula



I , wherein

A is N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, -C(S)R_2 or -C(O)R_2;

Z is NH, O, S, -N(C_1-C_2 alkyl) or -C($R_{13}R_{14}$), wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4)alkyl moieties in the foregoing R_1 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_9 wherein R_9 is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or -$CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$, -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro,

Sub A1 cont -

trifluoromethyl, amino, -(C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

or a pharmaceutically acceptable salt of such compound.

Sub A' cont.

3. A compound according to claim 2 wherein B is -NR_1R_2, -$NHCHR_1R_2$, -$SCHR_1R_2$ or -$OCHR_1R_2$; R_1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, or C_1-C_2 alkoxy group and may optionally contain one double or triple bond; and R_2 is benzyl or C_1-C_6 alkyl which may optionally contain one carbon-carbon double or triple bond, wherein said C_1-C_6 alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF_3, C_1-C_2 alkyl, or C_1-C_2 alkoxy.

4. A compound according to claim 2 wherein R_1 is C_1-C_6 alkyl which may be substituted by fluoro, CF_3, hydroxy, C_1-C_2 alkyl or C_1-C_2 alkoxy and which may optionally contain one carbon-carbon double or triple bond.

5. A compound according to claim 2 wherein R_2 is C_1-C_4 alkyl which may optionally be substituted by fluoro, chloro, CF_3, C_1-C_4 alkyl or C_1-C_4 alkoxy.

6. A compound according to claim 2 wherein R_3 is methyl, chloro, or methoxy.

7. A compound according to claim 2 wherein R_4 is methyl, -CH_2OH, cyano, trifluoromethoxy, methoxy, chloro, trifluoromethyl, -$COOCH_3$, -CH_2OCH_3, -CH_2Cl, -CH_2F, ethyl, amino or nitro.

8. A compound according to claim 2 wherein R_5 is phenyl substituted with two or three substituents.

9. A compound according to claim 2 wherein R_5 is pyridyl substituted with two or three substituents.

10. A compound according to claim 8 wherein said substitutents are selected, independently, from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may optionally be substituted with one hydroxy, C_1-C_4 alkoxy or fluoro group and which may optionally contain one carbon-carbon double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, and -(C(O)(C_1-C_4 alkyl).

11. A compound according to claim 9 wherein said substitutents are selected, independently, from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may optionally be substituted with one hydroxy, C_1-C_4 alkoxy or fluoro group and which may optionally contain one carbon-carbon double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, -COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, and -(C(O)(C_1-C_4 alkyl).

12. A compound according to claim 1, wherein said compound is

4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;

[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;

(N-(1-ethyl-propyl)-2-methyl-5-nitro-N□-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;

4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;

N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine; or

6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;

or a pharmaceutically acceptable salt of one of the above compounds.

13. A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13 for the treatment of a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human.

15. A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease, spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in

Sub A2 Cont.

chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.

16. A method according to claim 15 for the treatment of a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders, cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human.

17. A method of treating a condition comprising administering a compound of claim 1 in an amount effective to treat said condition, wherein said condition is selected from the group consisting of:

a) abnormal circadian rhythm;

b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and

c) emesis.

18. The method of claim 17 wherein the condition is abnormal circadian rhythm, and the compound is comined with a second compound useful for treating a sleep disorder.

19. The method of claim 18, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic

compounds, GABA brain receptor agonists, $5HT_2$ receptor antagonists, and D4 receptor binding .

20. The method of claim 17 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.

21. The method claim 17 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

22. The method of claim 21 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.

23. A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:

a) abnormal circadian rhythm;

b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and

c) emesis.

24. A pharmaceutical composition according to claim 23, wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

25. A pharmaceutical composition according to claim 24, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, $5HT_2$ receptor antagonists, and D4 receptor binding .

26. A pharmaceutical composition according to claim 23 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine,

clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.

27. A pharmaceutical composition according to claim 23 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

28. A pharmaceutical composition according to claim 27 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.

add A3

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